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Research Article *Pediatrics*

STUDY ON EFFICACY OF ARTESUNATE THERAPY IN SEVERE MALARIA IN PEDIATRIC PATIENTS AT TERTIARY CARE CENTRE

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A B S T R A C T

Objective: To describe the efficacy of artesunate therapy in severe malaria. **Material and method:** This was a single centre tertiary care hospital based prospective study. A total of 50 patients (age group 1 month- 18 years) of severe malaria admitted in PICU were enrolled in our study. The confirmation of malaria was done by blood smear for malarial parasite (PV/PF or both) or RDT (Rapid diagnostic test). **Results:** Most of patients 28% were in the age group 0f 6-10 years with mean age of 9.09 years. Among P. falciparum patients, 65.52% responded to artesunate rest were shifted to quinine therapy and in P. vivax patients 76.19% responded to artesunate therapy. Mean duration for fever clearance time on artesunate therapy was 37.92±21.33 hours,mean coma resolution time 22.73±20.19 hours, andmean parasite clearance time was 51.47±22.90 hours.In clinical outcome by artesunate therapy, in plasmodium falciparum 27(93.10%) patients were got cured and 2 patients (6.90%) died. In plasmodium vivax, 20 patients (95.24%) were cured successfully and 1 patient died. **Conclusion:** The emergence of resistant parasites to artesunate, as well as the lack of the short term availability of effective alternative ant malarial drugs, is of great concern in the fight against malaria.

INTRODUCTION

Malaria is a protozoal disease, transmitted by the bite of a female *anopheline* mosquito. It is the most important parasite disease in humans and common cause of fever in the tropics[1].
The WHO African Region accounted for most global causes of malaria(90%), followed by the South-East Asia Region (7%) and the Eastern Mediterranean Region(2%)[2]. South-East Asia(SEA) has been the harbinger of drug –resistant Plasmodium falciparum malaria. Starting with resistance to chloroquine, sulfadoxime + pyrimethamine, quinine, and mefloquine, this region has now produced parasites resistant to artimisinin. Antimalarial drug resistance emerges due to a spontaneous genetic change (mutation of gene amplification) in the malaria parasite. This mutation interferes with the parasite's susceptibility to drug.

In 2008, resistance to artemisinin was described in western Cambodia then subsequently, over the next few years, resistance spread to Thailand, Vietnam, Myanmar and Laos. It is proposed that the artemisinin-resistant parasites acquire the ability to quickly repair the damage caused by the drug. "K13 mutations thus became markers for artemisinin resistance.
At present, there are five accepted markers of artemisinin resistance, the therapeutic efficacy of ACT, the proportion of cases which are microscopy positive at day 3, parasite clearance half-life, ring stage survival assay, and K13 sequencing. The WHO has defined partial resistance as delayed parasite clearance following treatment with an artesunate monotherapy or with ACT.

Artemisinin-based combination treatments (ACT) became the mainstay of treatment for P. falciparum malaria since 2005 when the WHO advocated its use in National Malaria Programs. The rationale behind ACT is to achieve an improved barrier to drug resistance as multiple simultaneous mutations will be required for the parasite to become resistant[3].

MATERIAL AND METHOD

This was a single centre tertiary care hospital based prospective study conducted in department of Paediatrics, Balchikitsalaya M.B. Government Hospital, R.N.T. Medical College, Udaipur, Rajasthan, India from the month of July 2018 to July 2019 with prior approval from Institutional Ethics Committee. A total of 50 patients (age group 1 month- 18 years) of severe malaria admitted in PICU giving consent for the study by parents were included. The confirmation of malaria was done by blood smear for malarial parasite (PV/PF or both) positive by thick and thin smear or RDT (Rapid diagnostic test). In all included patient, a complete and detailed history, demographic profile with GPE, nutritional

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status were collected. All relevant systemic examination was done and laboratory investigations were sent.

Patients having severe manifestations of malaria were managed according to WHO protocol. They first given artesunate I.V. followed by a complete 3 day course of oral ACT once patient started to tolerate orally. Those patients who did not respond to artesunate clinically and parasitologicaly after 72 hours, were shifted to I.V. quinine based regimen as per the standard dose and administration guidelines. The 4 following parameters were monitored: Fever clearance time, Coma resolution time, Parasite clearance time and treatment failure to artesunate.

1) FCT (Fever clearance time): time required from initiation of therapy till the time patient become afebrile.
2) CRT (Coma resolution time): time required from initiation of therapy till the time patient get fully conscious.
3) PCT (Parasite clearance time): time interval from initiation of therapy to the first of three consecutive negative blood smear taken daily.

RESULTS

A total of 50 admitted patients with severe malaria, 28(56%) male and 22(44%) female were included in our study. Most of patients 14(28%) were in the age group of 6-10 years with a mean age of 9.09 years. In our study there were thirty three cases (66%) of >5 years had weight for height/BMI more than cut off point for malnutrition/under nutrition. Twelve patients (24%) (>5 years) were found undernourished. There were 5 children (<5 years) in our study fall into the criteria for severe acute malnutrition (SAM) including E-SAM. (Table-1)

Table1 Nutritional Status of the Patients

Nutritional status	No of cases	Percentage
Normal Wt. for Ht/BMI	33	66%
Malnourished/undernourished (Excluding SAM)	12	24%
Severe acute malnutrition (<5yr)	5	10%
Total	50	100%

In plasmodium falciparum, 19 patients (65.52%) responded to artesunate therapy, seven patients (24.14%) did not respond so they were shifted to quinine therapy. One patient (3.45%) was treated with mefloquine due to persistence of fever and parasitemia despite treatment with artesunate and quinine.
Out of 21 patients of plasmodium vivax malaria, 16(76.19%) responded to artesunate therapy. Four patients (19.05%) did not respond, hence they were shifted to quinine therapy. (Table-2)

Table 2 Failure of Artesuate Therapy in Study Population

	P. Falciparum No. of cases (%)	P. Vivax No. of cases (%)
Response	19(65.52%)	16(76.19%)
Shift to quinine	7(24.14%)	4(19.05%)
Other drug	1(3.45%)	0(0.00%)
Death	2(6.90%)	1(4.76%)
Total	29(100%)	21(100%)

One patient (9.09%) was shifted to quinine therapy within 48 hours, 3 patients (27.27%) shifted after 72 hours, 5 patients shifted after 96 hours, while 2 patients shifted on quinine therapy after 5 days. Out of these 2, one patient required mefloquine after 10 days due to failure to respond on quinine therapy. (Table-3)

Table 3 Change of Artesunate Due to Treatment Failure/ Deterioration

Duration	No. of cases (%)
>48 hours	1(9.09%)
>72 hours	3(27.27%)
>96 hours	5(45.45%)
>5 days	2(18.18%)
Total	11(100%)

Out of 17 undernourished and SAM patients, 12(70.6%) responded to artesunate, and 4(23.5%) patients were shifted to quinine therapy due to failure of treatment with artesunate. Only one patient expired. Similarly, out of 33 nourished patients, 24(72.72%) responded to artesunate, 7(21.21%) patients were shifted to quinine therapy, and two patients were expired. When the outcome of drug was compared with nutritional status, it was found statistically non-significant ($p>0.05$). (Table-4)

Table 4 Comparisons of Response to Artesunate Therapy In Undernourished/Sam Patients and Well Nourished Patients

Drug response	With malnutrition	Without malnutrition
Response to artesunate	12(70.6%)	24(72.72%)
Response to quinine	4(23.5%)	7(21.21%)
Expired	1(5.8%)	2(6.06%)
Total	17	33

In 23 patients (46%), fever clearance time by artesunate therapy was <24 hours. Fourteen patients (28%) had fever clearance between 24-48 hours. Four patients (8%) had fever clearance between 48-72 hours. Nine (18%) had fever clearance more than 72 hours. Mean duration for fever clearance time on artesunate therapy was 37.92±21.33 hours. (Table-5)

Table 5 Fever Clearance Time by Artesunate Therapy

Defervescence of fever	P. falciparum No.of cases (%)	P.vivax No.of cases (%)	Total (%)
<24 hours	13(44.83%)	10(47.62%)	23(46%)
24-48 hours	8(27.59%)	6(28.57%)	14(28%)
48-72 hours	3(10.34%)	1(4.76%)	4(8%)
Fever persisted beyond 72 hours	5(17.24%)	4(19.05%)	9(18%)
Total	29(100%)	21(100%)	50(100%

Most of patients 18(41.86%) regained consciousness within 24-48 hours, 16(37.21%) regain consciousness within 24 hours. In 5 patients (11.63%) comatose condition was persisted for 48-72 hours and remaining 4 patients regained consciousness after 72 hours of artesunate therapy. Mean

duration for coma resolution time was 22.73±20.19 hours. (Table-6)

Table 6 Coma Resolution Time in Study Population

Time to regain consciousness	P.falciparum No.of cases (%)	P.vivax No.of cases (%)	Total (%)
<24 hours	10(47.62%)	6(27.27%)	16(37.21%)
24-48 hours	7(33.33%)	11(50.00%)	18(41.86%)
48-72 hours	2(9.52%)	4(18.18%)	6(13.95%)
>72 hours	2(9.52%)	1(4.55%)	3(6.98%)
Total	21(100%)	22(100%)	43(100%)

In most of patients 19(48.72%) with artesunate therapy, parasitemia cleared in 24-48 hours. In 5 patients (12.82%) parasites disappeared from blood within 24 hours whereas in 5(12.82%) it took 48-72 hours for clearance of parasitemia. In 7 patients (17.95%) didn't show parasite clearance even after 3-5 days of artesunate therapy. Mean parasite clearance time was 51.47±22.90 hours. (Table-7)

Table7 Parasite Clearance Time

Disappearance of parasitemia	No. Of patients	Perentage
<24 hours	5	12.82%
24-48 hours	19	48.72%
48-72 hours	5	12.82%
3-5 days	3	7.69%
No	7	17.95%
Total	39	100%

In clinical outcome by artesunate therapy, in plasmodium falciparum 27(93.10%) patients were got cured and 2 patients (6.90%) died.In plasmodium vivax, 20 patients (95.24%) were cured successfully and 1 patient died.

DISCUSSION

In the present study, 50 patients were studied, and among them 56% were males and 44% were female. Maximum numbers of cases (28%) was observed in age group of 6-10 years of age. There were 16% cases of less than 1 year of age. Mean age of affected children was 9.09 years. The sex incidence with predominance of male children is in conformity with general hospital trends of overall admission in this age group. Low incidence of malaria observed in children less than 1 year of age can be attributed to transplacentally acquired humoral immunity by babies and sole milk diet which is deficient in PABA.

In our study 33 cases (66%) were nutritionally healthy. In the age group 5-18yr, 24% patients were undernourished. There were 5 patients (10%) of severe acute malnutrition (<5yeras) also. Wendy J. **Verret *et al* (2011)** [4] have assessed the association between malnutrition and malaria risk. In a cross-sectional study in Kenya of 1,862 children under 36 months of age, stunted children were more likely to have parasitemia (odds ratio 1.98) and clinical malaria (odds ratio 2.65) than non stunted children. Likewise, a prospective cohort study of 487 children under 5 years of age in the Gambia found that stunted children were at higher risk for malaria than non stunted children.

In plasmodium falciparum 70.6% responded to artesunate therapy, 24.4% patients did not respond so they were shifted quinine therapy and one patient shifted on mefloquine because of persistence of parasitemia and fever. Out of 21 patient of plasmodium vivax, 76.19% responded to artesunate treatment. Four patient 19.05% were shifted to quinine therapy. According to WHO report 2018 artemisinin resistance is defined as delayed parasite clearance following treatment with an artesunate monotherapy or with an artemisinin-based combination therapy (ACT). This led to a change in treatment policy to artemether-lumefantrin in the northeastern region of the country. Despite the delayed response to artemisinin in some area of the GMS, ACTs remain the most effective treatment for uncomplicated falciparum malaria.

In our study out of 17 undernourished/SAM patients, 70.6% responded to artesunate, 23.5 % were shifted to quinine and one patient expired. Similarly out of 33 nourished patient 72.72%responded to artesunate, 21.21 % were shifted to quinine and two patients expired. The efficacy of drug doesn't vary with the nutritional status of patient. When the outcome of drugs was compared with nutritional status it was found to be statistically non-significant (P>0.05). Leang *et al.* (2019)[5] showed artesunate given in combination had better results. Pyronaridine-artesunate has high efficacy in eastern Cambodia and it could be used to increase the diversity of antimalarial therapy in the region. One patient was shifted on quinine within 48 hours, 3 shifted after 72 hours, 5 shifted after 96 hours while two patients shifted on quinine after 5 days. Out of these, 2 patient required mefloquine after 10 days.

In 23 patients (46%), fever clearance time by artesunate therapy was <24 hours. Fourteen patients (28%) had fever clearance between 24-48 hours. Four patients (8%) had fever clearance between 48-72 hours. Thirteen patients (26%) had fever clearance more than 48 hours. Mean duration for fever clearance time was 37.92±21.33 hours. When the difference in mean FCT compared between p. falciparum and p. vivax, it was statistically non-significant (p>0.05).Similar to our study Singh A *et al*. (2015)[6] showed that fever duration was less than 48 hours in 50% cases of artesunate group. The mean duration of fever was 37.29 ± 21.33 hours in quinine group and 39.0 ± 18.53 hours in artesunate group. Karbwang *et al***.** (1995)[7] found mean fever deffervescence time to be 79 hours in artemisinin derivative treated patients. Nayak *et al*. (2011)[8] reported that mean fever clearance time with artesunate was 2.17 day.

Eighteen patients (41.86%) regained consciousness within 24-48 hours, 16(37.21%) regain consciousness within 24 hours. In 5 patients (11.63%) coma persisted for 48-72 hours and remaining 4 patients regained consciousness after 72 hours of artesunate therapy. Mean duration for coma resolution time was 22.73±20.19 hours. When CRT in P. falciparum and P. vivax were compared the mean difference was found to be statistically non-significant (p>0.05). Nayak *et al*. (2011) reported that mean CRT with artesunate was 1.33 day. Nandeshwar *et al*. (2015)[9]done efficacy assessment of artesunate v/s quinine, and it shows that CRT was statistically less in quinine group (25.80 hours) compared to artesunate group (42 hours). Mohanty AK *et al*. (2004)[10] in there study also showed that mean CRT was 50.4 ± 31.48 hours with artesunate treated patients.

In response to artesunate therapy 12.82% patients shows parasite clearance within 24 hours, 19 patients (48.72%) between 24-48 hours, 5 patients (12.82%) between 48-72 hours and 3 patients had parasite clearance between 3-5 days.

Seven (17.95%) patients didn't show parasite clearance even after 5 days of artesunate. Mean parasite clearance time was 51.47±22.90 hours. When the difference in mean PCT was compared between P. falciparum and P. Vivax, it was found statistically non-significant (p>0.05). Nandeshwar *et al*. (2015)[9]in there study reported that, mean PCT was 39.72 hours with artesunate treatment. Nayak *et al*. (2011)[8]stated that mean PCT was 1.62 days with artesunate therapy in there study. Mohanty *et al*. (2004)[10] showed that mean PCT was 41.67± 16.78 hours with artesunate treatment.

In clinical outcome by artesunate therapy, in plasmodium falciparum 27(93.10%) patients were got cured and 2 patients (6.90%) died. In plasmodium vivax, 20 patients (95.24%) were cured successfully and 1 patient died. Nayak *et al*. (2011)[8] found that to give artesunate as compared to quinine was easy. Out 65 patients who were treated with artesunate all were cured successfully no mortality recorded. Dondrop A (2005)[11] in their study reported that mortality was 12% with artesunate therapy.

CONCLUSION

The emergence of resistant parasites to artesunate, as well as the lack of the short term availability of effective alternative antimalarial drugs, is of great concern in the fight against malaria. Inour study, 50 patients of severe malaria, 7(28%) had treatment failure with artesunate therapy. Out of these, 6 patients respond to quinine therapy which shows that quinine is still effective and lifesaving drug, though in our study we didn't compare the side effects of both the antimalarial drugs.
Conflict of interest-None

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Ethical approval: Study was approved by the Institutional Ethics Committee

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